From bioactive pyrrolidino[3,4-*c*]pyrrolidines to more bioactive pyrrolidino[3,4-*b*]pyrrolidines *via* ring-opening ring-closing promoted by sodium methoxide

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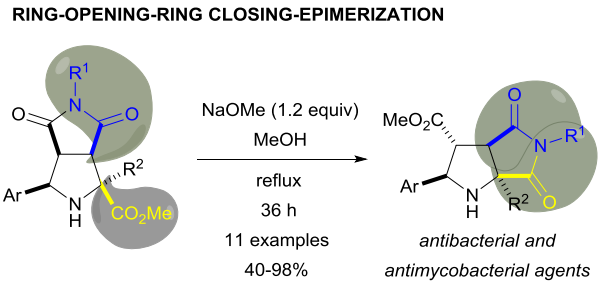

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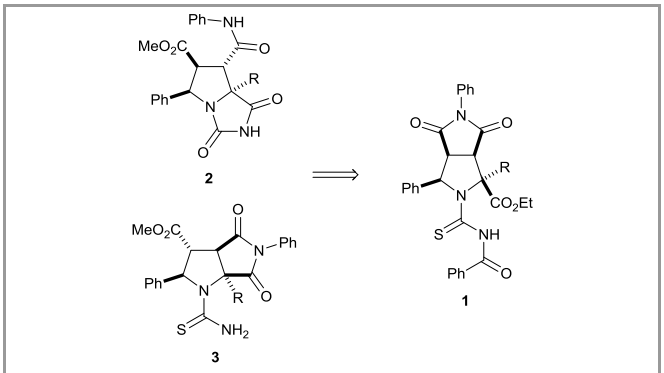
Abstract The process involving a rearrangement of pyrrolidino[3,4-*c*]pyrrolidine to another pyrrolidino[3,4-*b*]pyrrolidine involving sodium methoxide as base is fully studied. The effects of the substituents are analyzed during the ring-opening ring-closing sequence. Computational studies are also performed to explain the importance of susbstituents and quaternary carbons, especially when the (3-indolyl)methyl is present in the starting material. Finally, all the samples are evaluated as potential candidates as antibacterial and antimycobacterial agents.

Key words cycloaddition • azomethine ylides • rearrangement • antibacterials • DFT calculations

Introduction

The design of very simple molecular architectures with the broadest biological and medicinal coverage is always pursued, and especially for the long treatment of degenerative illnesses. A clear example is represented by succinimides.[1] Activities such as CNS depressant, analgesic, antitumor, antispasmodic, bacteriostatic, hypotensive, antibacterial, antifungal, anti-tubercular, etc., have been reported in the literature.[1,2,3] Succinimides are easily available from succinic acid or succinic anhydride and their derivatives involving ring-opening/ring-closing strategies.[1,4] However, the imido group and the double bond of maleimides offer new substitution patterns. For example, their electrophilic character made them excellent dienophiles in Diels-Alder reactions and dipolarophiles in 1,3-dipolar cycloadditions.[5] In fact maleimides are frequently used for the optimization of this cycloaddition processes.

During our investigation of the synthesis of new derivatives with a thiohydantoin framework[6] (similar to **2**) with anti-tuberculosis and anti-bacterial activity,[7,8] we discovered the formation of unexpected compounds, which resulted from a rearrangement of the succinimide in the presence of sodium methoxide. The result of this rearrangement is a chemical switch in which from one fused succinimide with a tetrahydropyrrolo[3,4-*c*]pyrrole skeleton **1** it was possible access to a new succinimide with tetrahydropyrrolo[3,4-*b*]pyrrole framework **3** (Scheme 1).



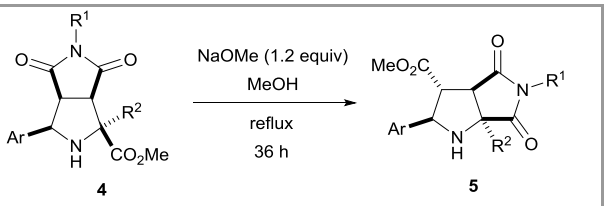
Scheme 1 First evidence of the titled succinimide rearrangement

In this work we thoroughly study the mechanism of the particular rearrangement originated by the methoxide anion, which attack to molecules **4** to give products **5** (Scheme 2).[6] We envisage the possible scope and its utility in synthetic organic chemistry and as antituberculosis and antibacterial agent.[7]

Results and Discusion

Scope of the rearrangement and structural determination of compounds 5, 6 and 7.

Following the reaction conditions found in the confirmation of the structure of compound **5** (Ar, R^1 = Ph, R^2 = 3-indolyl) in our previous publication,[6] we started with the analysis of the tetrahydropyrrolo[3,4-*c*]pyrrole **4a** obtained from 1,3-dipolar cycloaddition of the corresponding methyl benzylideneaminoglycinate with *N*-methylmaleimide (NMM), (see experimental part). Under general conditions described in Scheme 2, compound **4a** afforded a very complex mixture of unidentified products detected by ^{1}H NMR experiment of the crude reaction mixture.



Scheme 2 Succinimide rearrangement studied in this work

Cycloadducts **4b**-**4f**, obtained from imino esters derived from leucine and phenylalanine were submitted to conditions depicted in Scheme 2, obtaining the corresponding tetrahydropyrrolo[3,4-*b*]pyrroles **5b-f** in moderate yield (up to 54%, Figure 1). Despite purifying all these compounds in deactivated flash silica gel, we observed some decomposition/epimerization during this process. We also discovered that they were not stable under storage for more than one week at -20 °C.

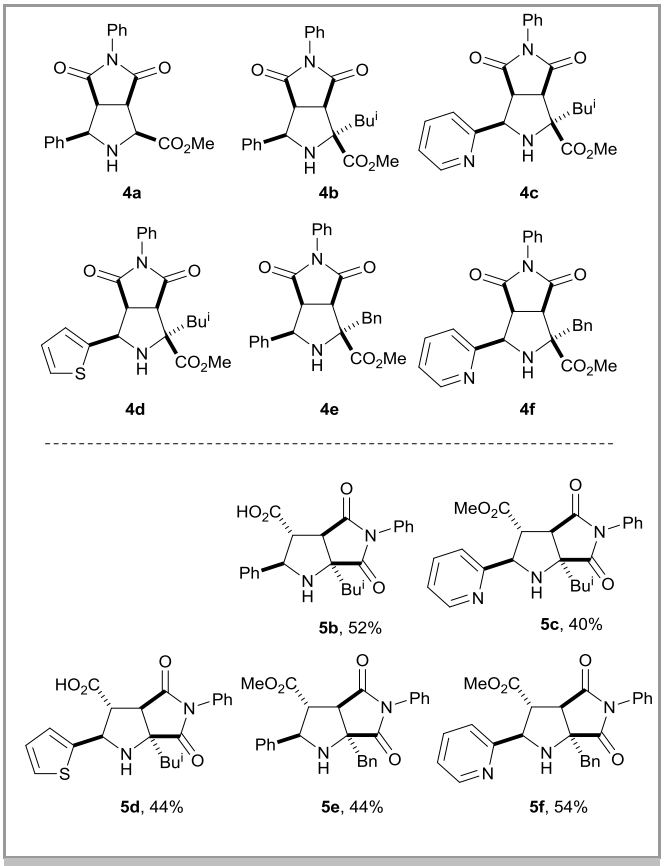
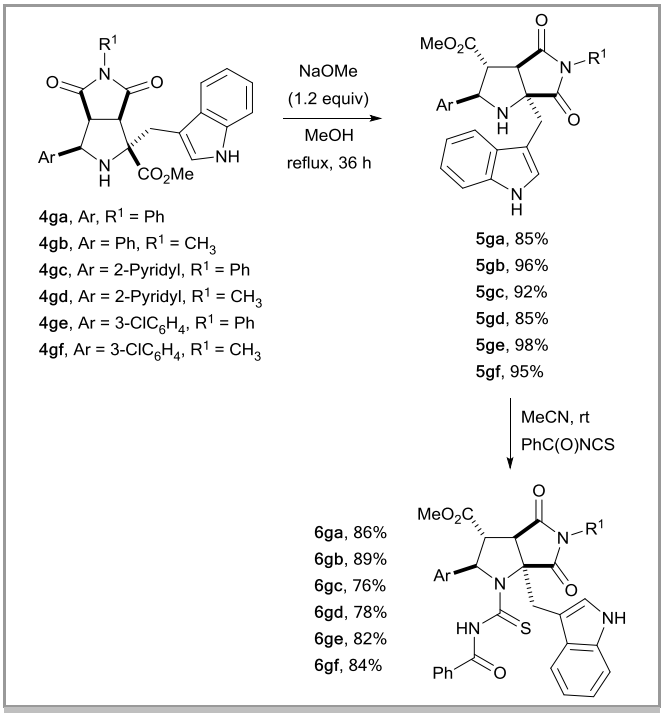


Figure 1 Succinimide rearrangement observed in compounds **4a**-**4f**

According to our experience,[8] the introduction of an indol ring can be beneficial for increasing the biological effect of the substance.[9] With this aim, cycloadducts **4g**, derived from tryptophan, were prepared (see experimental part) and were allowed to undergo the titled stereospecific rearrangement. Again, the reaction proceeded regio- and stereospecifically to give the corresponding compounds **5g**[10] in very high yields (70-98 %) (Scheme 3). These series of molecules **5g** are very stable and could be stored for a long time.

The preparation of *N*-benzoylcarbothioamides **6g** was achieved smoothly by reaction of **5g** with benzoylisothiocyanate in acetonitrile at room temperature for 24-30 h (Scheme 3). The incorporation of this unit to the pyrrolidine ring increases the biological potency of the precursor heterocycles.



Scheme 3 Synthetic **4g**→**5g**→**6g** sequence involving (3-indolyl)methyl derivatives

The relative configuration of all new racemic compounds was stablished according to data acquired using NMR experiments and by single crystal X-ray diffraction analysis for the compound **6gf** (Figure 2).

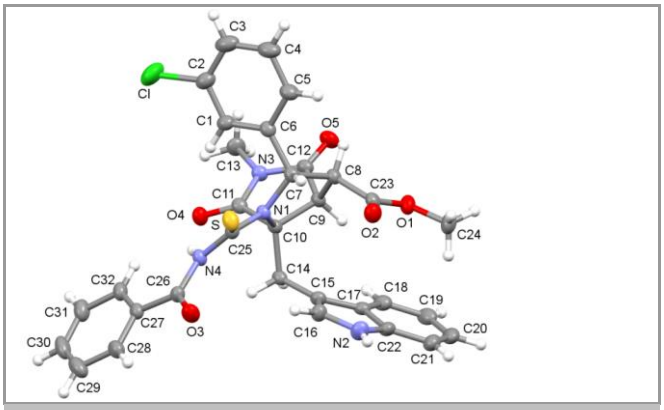
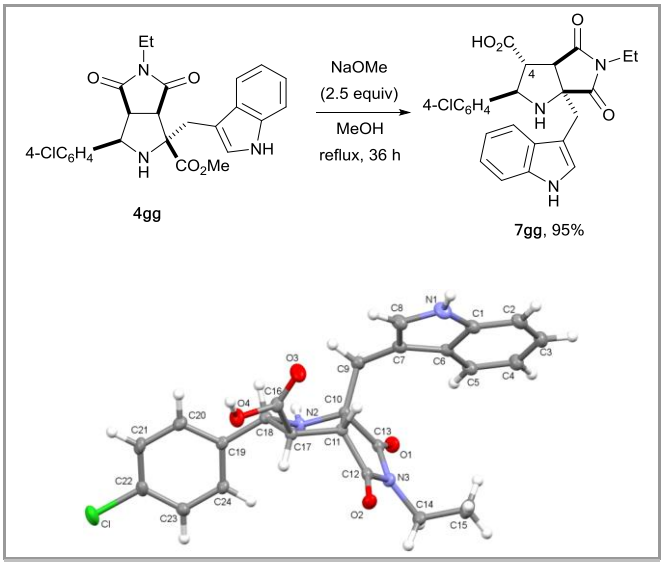


Figure 2 X-Ray diffraction analysis of compound **6gf**. Thermal ellipsoids are drawn at 40% probability level.[11]

A larger excess of sodium methoxide in methanol (not dry) furnished the same arrangement (under identical reaction conditions) afforded free betaproline amino acid[12] derivative (possessing a zwitterionic structure) **7gg** in almost quantitative yield (Scheme 4). The structure of its skeleton was also confirmed by X-ray diffraction analysis demonstrating that epimerization occurred only in the carbon atom 4.



Scheme 4 Sythesis of betaproline derivative **7gg** and its X-ray diffraction analysis pattern.[13]

Study of the mechanism by DFT calculations.

At this point we can argue that the presence of a quaternary carbon at 2-position in the prolinate ring of compounds **4** seems to be crucial for the development of the arrangement in basic media. The Thorpe-Ingold effect can justify the scarce reactivity of cycloadduct **4a** and the moderate to excellent yields achieved in substrates **4b**-**g**. Additionally, the presence of the (3-indolyl)methyl residue at this position accelerated the process and gave an extra stability to the final compounds. We decided to perform computational calculations within the DFT framework in order to better understand the reaction mechanism associated with succinimide **4** rearrangement and its subsequent isomerization to yield compounds **5**. For that, we selected **4ga** as model compound. In the first part of this study we analyzed all the possible reactions of methoxide anion with **4ga**. This anion can act as a nucleophile, reacting with the CO double bond of the imido groups (**TS1** and **TS1'** in Figure 4). On the other hand, methoxide can also act as base, therefore the abstraction the protons in α position of the imido groups of maleimide moiety were also considered (Figure 3).

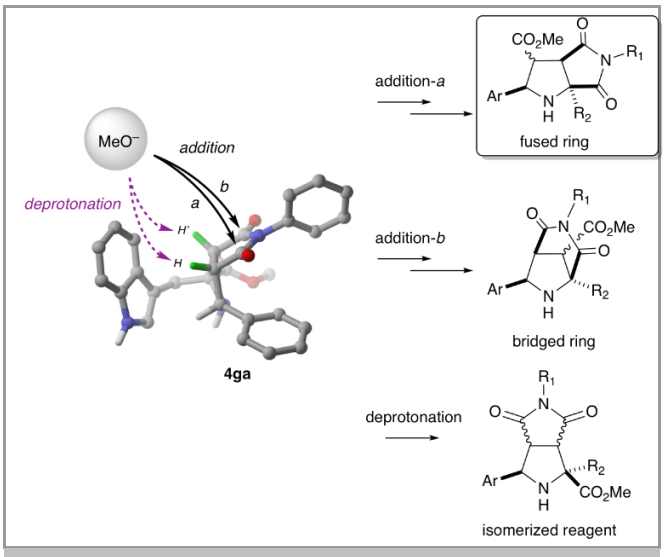


Figure 3 Possible reactions of compound **4ga** with methoxide anion. Acidic hydrogens considered are highlighted in green

The main geometrical features of the transition structures associated with these processes and their relative energies are collected in Figure 4.

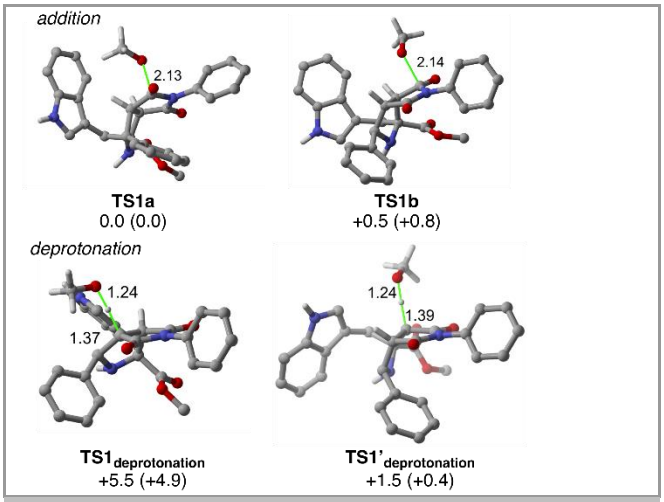
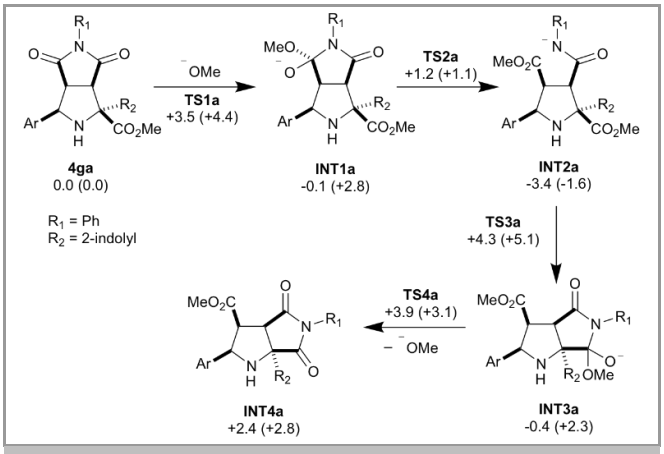


Figure 4 Main geometrical features and relative activation and free Gibbs energies (between brackets) associated with the possible reactions of methoxide anion with computed at B3LYP-D3(PCM)/6-31+G* level at 298.15 K. Distances and energies are in Å and kcal mol^{-1}, respectively. Non-relevant hydrogen atoms are omitted for clarity

Our calculations shown that the activation energy barriers associated with the methoxide addition are lower than the deprotonation ones. This difference is even smaller considering Gibbs free activation barriers. However, the corresponding enolates formed are high in energy, consequently, their formation is thermodynamically disfavored. Therefore, any possible isomerization of compound **4ga** via direct proton abstraction will not be further considered in this study. In addition, calculations also show that bridged ring formation is also kinetically disfavored (See supporting information for further details about other possible reaction paths computationally analyzed). Within these results, we next analyzed the succinimide rearrangement processes leading towards formation of fused rings **5**. The relative and activation energies (and Gibbs free energies) computed are collected in Scheme 5. The main geometrical features of the corresponding transition structures are depicted in Figure 5.



Scheme 5 Activation and relative energies (and Gibbs free energies between brackets) associated with **4ga** rearrangement with methoxide anion computed at B3LYP-D3 / 6-31+G(d) level of theory at 298 K. Energies are in kcal mol^{-1}

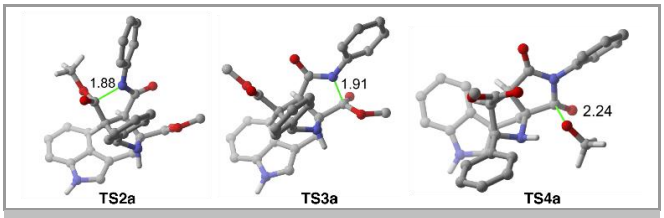
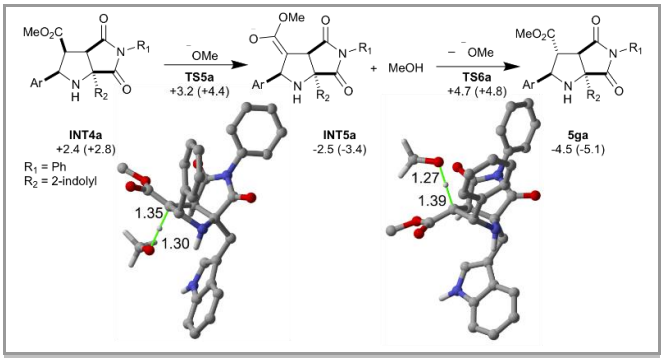


Figure 5 Main geometrical features and relative activation and free Gibbs' energies (between brackets) associated with **4ga** rearrangement. See caption of Figure 3 for further details

Within the proposed mechanism, formation of the new maleimide ring is the rate-limiting step (**TS3a** has activation barrier ca. 1 kcal mol^{-1} higher than any other step). Moreover, calculations show that formation of **INT4a** is thermodynamically disfavored.

Once formation of **INT4a** via ring–opening ring–closing mechanism was assessed, we next analyzed computationally the subsequent isomerization towards ring–fused **5ag**. Relative and activation energies (and Gibbs free energies) and main geometrical features of the corresponding transition structures are collected in Scheme 6.



Scheme 6 Activation and relative energies (and Gibbs free energies between brackets) associated with **5ga** formation. See caption of Figure 3 for further details

Our calculations indicate that the isomerization of **INT4a** towards **5ga** formation is thermodynamically favored, as reflected by its stability. Geometry inspection revealed that **INT4a** is highly energetic structural arrangement due to the repulsion associated with the eclipsed conformation of methoxycarbonyl and maleimide moieties. That repulsion is dismissed due to the isomerization process, being replaced by a stabilizing π,π-stacking interaction with the 3-indolyl moiety, and a close indole-ester hydrogen bonding, thus making this step the driving force of the reaction (Figure 6). Remarkably, the activation barriers associated with the proposed mechanism are lower than 6 kcal mol^{-1}, compatible with the relatively mild conditions experimentally required (reaction temperature of 65 °C). These stabilizing interactions, which did not exist in compounds **5b-f**, can be the reasons of the epimerization/decomposition of these last molecules.

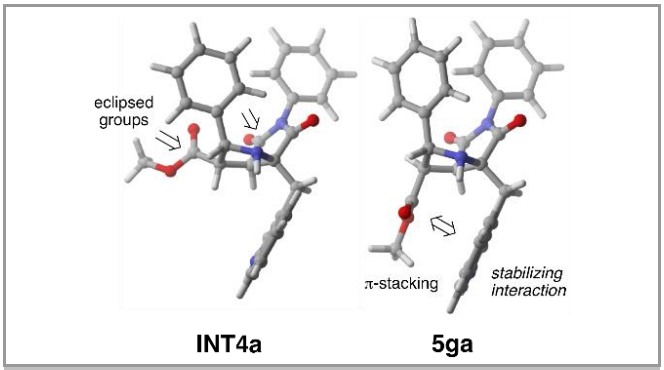


Figure 6 Optimized structures of **INT4a** and **5ga**

Anti-mycobacterial Activity.

Anti-mycobacterial activity of prepared compounds were tested against *M. tuberculosis* H37Rv strain using Microplate Alamar Blue assay according to literature method[14] measured by means of MIC values (μg/mL). Ethambutol (EMB) (Sigma E4630) and isoniazid (INH) (Sigma I3377) were used as standard reference drugs. The Anti-TB activity against *M. tuberculosis* H37Rv strain showed moderate activity, in the range of 10-80μg/mL, when compared to isoniazid and ethambutol as known reference drugs (Table 1). Especially the compounds **4gf** (possess -Cl on the phenyl ring and -Me on the melaimide ring) revealed the highest activities with the MIC values of 10 μg/mL whereas the compound **4ga**, **4gc**, **4ge**, **6gd** and **7gg** showed activity in value of 20-40 μg/mL and the others compounds showed the lowest activities with the MIC values of 80 μg/mL. In addition the tested compounds exhibited better anti-TB activity when compared their anti-bacterial activity as indicated in Table 1. Although the mode of action or biological target of these molecules is unknown at the moment, further work to get more potent derivatives is under investigation.

Anti-bacterial Activity.

Antibacterial activity of prepared compounds were tested against two Gram(+) bacteria *Staphylococcus aureus* (ATCC 25925), *Bacillus subtilis* (ATCC 6633) and three Gram(-) bacteria *Escherichia coli* (ATCC 25923), *Acinetobacter baumannii* (ATCC 02026), *Aeromonas hydrophila* (ATCC 95080) which obtained from the Refik Saydam Hıfzısıhha Institute, Ankara, Turkey. Ampicillin was used as control drug. The minimum inhibitory concentrations (MIC) values was determined by agar dilution in duplicate as recommended by the Clinical Laboratory Standards Institute.[15] To ensure that the solvents had no effect on microbial growth, a control test was performed containing inoculated broth supplemented with DMSO at the same dilutions used for the test compounds and was determined to be inactive.

The tested compounds inhibited the growth of bacteria at MIC values in the range of 62.5-500 μg/mL whereas the control, ampicillin, showed activity against the tested bacterıa with a range of 125-0.9 μg/mL as given in Table 1. It is also important to note that the screened compounds were found to show the better activity against *A.baumannii* (ATCC 02026) in the range of 62.5-125 μg/mL whereas the control ampicillin showed activity in MIC values of 125 μg/mL.

Table 1. The MIC values (μg/mL) of the tested compounds against the bacterial and mycobacterial strains.

	S. aureus (ATCC 25925)	*E. coli* (ATCC 25923)	*A. baumannii* (ATCC 02026)	*B. subtilis* (ATCC 6633)	*A. hydrophila* (ATCC 95080)	*M. tuberculosis* H37Rv
4ga	250	125	62,5	125	125	20
4gb	125	125	125	125	125	80
4gc	125	125	62,5	125	125	40
4gd	250	125	62,5	125	125	80
4ge	125	125	62,5	125	125	40

4gf	125	125	62,5	62,5	62,5	10
5gd	125	125	62,5	125	62,5	80
6ga	125	125	125	125	125	80
6gb	250	250	125	250	250	80
6gd	250	250	125	250	500	31.25
6ge	125	125	125	125	125	80
6gf	125	250	125	125	125	80
7gg	62,5	125	62,5	125	62,5	40
Ampicillin	31.25	15.62	125	0.9	31.25	
Isoniazid						0.2 and 0.1
Etambuol						5 and 10

Conclusions

The rearrangement of tetrahydropyrrolo[3,4-*c*]pyrrole skeleton to a new tetrahydropyrrolo[3,4-*b*]pyrrole structure could be efficiently controlled in basic media. The presence of quaternary carbons in the starting bicyclic succinimide favored the rearrangement. The presence of the (3-indolyl)methyl group attached to this quaternary carbon is crucial for the stability of the final rearranged succinimides, increasing the biological activity of this family of compounds. Calculation predictions were in agreement with the experimental findings: first, the methoxide anion attacked the carbonyl group rather than promote the deprotonation; second, the spontaneous isomerization afforded a much more stable compound; third, a stabilizing π-stacking interaction between the indole ring and the ester group bonded to the epimerized carbon atom was the driving force of the reaction. Compound **4gf** was the most active compound after the evaluation of all biological tests.

Experimental Section

The commercially available reagents for syntheses and analyses were obtained with analytical grade and used as received. Column chromatography was performed on silica gel 60 (Merck, 230-400 mesh). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Mass spectra were obtained using a Bruker AC-300 or AC-400, and were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR using $CDCl_3$ and MeOD as a solvent. Chemical shifts are given in parts per million (δ:) downfield from tetramethylsilane. The following abbreviations are used: s – singlet; d – doublet; t – triplet; q – quartet; m – multiplet; br – broad. IR spectra were taken on a Perkin-Elmer Spectrum One FT-IR spectrometer and also were taken on Nicolet 510 P-FT. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in m/z are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S.The compounds are named according to the IUPAC system; names were obtained using MDL Autonom.

The known pyrrolidine derivative methyl (1S,3R)-1-((1H-indol-3-yl)methyl)-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **(4ga)** and and aminocarbothiol pyrrolidine derivatives (2*S*,3*S*,3a*S*,6a*R*)-Methyl 6a-((1*H*-indol-3-yl)methyl)octahydro-4,6-dioxo-2,5-diphenylpyrrolo[3,4-*b*]pyrrole-3-carboxylate **(5ga)** were prepared as from literature. [16,6]

Novel bicyclic pyrrolidine derivatives **4gb-4gf** were prepared by modification of literature methods.[17,6]

Computational Methods

Theoretical calculations have been carried out at the B3LYP-D3/6-31+G(D)[18] level by using the GAUSSIAN 09[19] suite of programs. Activation and relative (Gibbs) energies were computed within the DFT framework[20] at the B3LYP-D3/6-31+G(D) level at 298K in which dispersion corrections are included by means of Grimme's D3 model.[21] Solvent effects were estimated by the polarization continuum model[22] (PCM) method within the self-consistent reaction field (SCRF) approach.[23] All SCRF-PCM calculations were performed using dimethylsulfoxide (ε= 46.826) as model solvent. Merz-Kollman atomic radii cavities (as invoked by the radii= Pauling keyword) were used in reaction steps associated with hydrogen atom migration.

All the stationary points were characterized by harmonic vibrational analysis. Local minima showed positive definite Hessians. Fully optimized transition structures (TSs) showed one and only one imaginary frequency associated with nuclear motion along the chemical transformation under study. Reaction paths were checked by Intrinsic Reaction Coordinate (IRC) calculations. In order to avoid errors associated with 1N solvation state, activation barriers were compute comparing energies of directly connected stationary points.

General procedure for Preparation of pyrrolidines

To a solution of the silver salt (AgOAc) in toluene (3 mL) was added a solution of imino ester (1 mmol) and *N*-phenylmaleimide (1 mmol) in toluene (2 mL). To the resulting suspension trimethylamine (0.05 mmol, 7 μL) was added and the mixture stirred at room temperature (20-30 ºC) for 18-24 h. The crude reaction mixture was filtered through a small Celite path. The residue was purified by flash chromatography or the solid products were recrystallized in mixture of *n*-hexane/ether.

General procedure for rearrangement access to pyrrole-4,6-diones

To a stirred solution of bicyclic pyrrolidine **4a-4f** (1 mmol) in dry methanol (10 mL) was added dropwise a solution of sodium methoxide (1.2 mmol) in dry methanol (10 mL) over 10-15 min, and the mixture stirred and refluxed for 32-36 h. The solvent was evaporated under reduced pressure and quenched with saturated aqueous ammonium chloride, then extracted with dichloromethane (3x15 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The product **5b-5f** were purified by flash chromatography, the silica gel was deactivated (a 5% of triethylamine was added as co-eluent) to improve the yield of the final product.

Methyl (1S,3R,3aS,6aR)-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4a): After 18 hours and work up the product was isolated as a white solid (318 mg, 91 % yield); column chromatography (*n*-hexane:EtOAc; 8:2); All spectra were in agreement with reported data.

Methyl (1S,3R,3aS,6aR)-1-isobutyl-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4b): After 18 hours and work up the product was isolated as a white solid (321 mg, 79 % yield); column chromatography (*n*-hexane:EtOAc; 8:2); mp: 145-149 ºC; IR (ATR) υ_{max}: 1713, 1502, 1375, 1206, 1166, 1140, 854, 702, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 1.69-1.87 (m, 2H), 2.01-2.19 (m, 1H), 2.81 (d, *J* = 7.2 Hz, 1H, NH), 3.38 (d, *J* = 7.6 Hz, 1H), 3.76 (dd, *J* = 9.3, 7.6 Hz, 1H), 3.83 (s, 3H, OCH_3), 4.72 (dd, *J* = 9.2, 7.1 Hz, 1H), 7.01-7.10 (m, 2H, Ar-H), 7.25-7.48 (m, 8H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2 (CH_3), 24.4 (CH_3), 24.7 (CH), 43.2 (CH_2), 50.3 (CH), 52.5 (CH_3), 56.4 (CH), 62.3 (CH), 70.5 (C), 126.1, 127.2, 128.5, 128.6, 128.7, 129.1, 131.6, 137.1 (Ar-C), 172.8 (C=O), 173.8 (C=O), 174.8 (C=O) ppm; MS (EI): m/z 350 (M^+-C_4H_9, 21%), 349 (50), 347 (100), 233 (16), 202 (10), 190 (50), 170 (11), 147 (11), 143 (13), 130 (14), 115 (10), 103 (15). HRMS (DIP): m/z [M^+] calculated for $C_{24}H_{26}N_2O_4$, 406.1893; found: 406.1905.

Methyl 6a-isobutyl-4,6-dioxo-2,5-diphenyloctahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5b): After 36 hours and work up the product was isolated as a sticky yellow oil (211 mg, 52 % yield); column chromatography (silica gel deactivate with 5% Et_3N) (*n*-hexane:EtOAc; 8:2); IR (ATR) υ_{max}: 29254, 2922, 1709, 1495, 1378, 1235, 1191, 734, 702, 690, 617, 586 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.79-1.98 (m, 2H), 2.10-2.19 (m, 1H), 3.64 (dd, *J* = 4.7, 3.3 Hz, 1H), 3.76 (d, *J* = 3.3 Hz, 1H), 3.79 (s, 3H, OCH_3), 4.79 (d, *J* = 4.7 Hz, 1H), 6.80-6.90 (m, 2H, Ar-H), 7.23-7.67 (m, 8H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4 (CH_3), 24.3 (CH_3), 25.6 (CH), 43.2 (CH_2), 51.2 (CH), 52.9 (CH_3), 54.7 (CH), 65.8 (CH), 69.9 (C), 126.4, 128.1, 128.8, 128.9, 129.1, 131.8 (Ar-C), 173.1 (C=O), 175.9 (C=O), 178.2 (C=O) ppm; MS (EI): m/z 350 (M^+-C_4H_9, 36%), 318 (13), 200 (94), 191 (20), 177 (100), 171 (13), 144 (21), 143 (14), 119 (14), 91 (21). HRMS (DIP): m/z [M^+] calculated for $C_{24}H_{26}N_2O_4$, 406.1893; found: 406.1868.

Methyl 1-isobutyl-4,6-dioxo-5-phenyl-3-(pyridin-2-yl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4c): After 18 hours and work up the product was isolated as a white solid (350 mg, 86 % yield); column chromatography (*n*-hexane:EtOAc; 6:4); mp: 171-175 ºC. IR (ATR) υ_{max}: 1705.7, 1387, 1248, 1207, 1151, 1181, 764, 728, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, *J*= 6.6 Hz, 3H), 1.01 (d, *J*= 6.7 Hz, 3H), 1.69 (dd, *J*= 14.1, 4.7 Hz, 1H), 1.81-1.97 (m, 1H), 2.16 (m, 1H), 3.46 (d, *J* = 7.6 Hz, 1H), 3.70 (dd, *J* = 9.0, 7.6 Hz, 1H), 3.86 (s, OCH_3), 4.70 (d, *J* = 9.0 Hz, 1H), 7.02-7.25 (m, 3H, Ar-H), 7.30-7.49 (m, 4H, Ar-H), 7.68-7.73 (m, 1H, Ar-H), 8.34-8.65 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1 (CH_3), 24.4 (CH_3), 25.0 (CH), 44.3 (CH_2), 51.7 (CH), 52.6 (CH_3), 58.5 (CH), 65.0 (CH), 72.2 (C), 123.7, 123.9, 126.6, 128.7, 129.1, 131.9, 136.9, 149.4, 155.5 (Ar-C), 172.33 (C=O), 174.5 (C=O) 174.8 (C=O) ppm; MS (EI): m/z 408 (M^+ 12%), 407 (47), 351 (14), 350 (24), 349 (23), 348 (100), 177 (10), 175 (41), 171 (17), 145 (18), 131 (13). HRMS (DIP): m/z [M^+] calculated for $C_{23}H_{25}N_3O_4$: 407.1845; found: 407.1851.

Methyl 6a-isobutyl-4,6-dioxo-5-phenyl-2-(pyridin-2-yl)octahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5c): After 37 hours and work up the product was isolated as a sticky yellow oil (157 mg, 40 % yield); column chromatography (silica gel deactivate with 5% Et_3N) (*n*-hexane:EtOAc; 6:4); IR (ATR) υ_{max}: 3321, 2957, 2925, 1709, 1593, 1375, 1191, 1138, 749, 690, 599 cm^{-1}; ^1H NMR (300 MHz, MeOD): δ 0.94 (d, *J*= 6.5 Hz, 3H), 1.02 (d, *J*= 6.6 Hz, 3H), 1.72-1.99 (m, 2H), 2.02-2.23 (m, 1H), 3.79-3.83 (m, 1H), 3.93 (d, *J* = 2.7 Hz, 1H), 4.93 (d, *J* = 3.3 Hz, 1H), 6.73-6.94 (m, 2H, Ar-H), 7.20-7.43 (m, 4H, Ar-H), 7.60 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.69-7.74 (m, 1H, Ar-H), 8.40-8.46 (m, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, MeOD): δ 24.0 (CH_3), 24.7 (CH_3), 26.5 (CH), 45.4 (CH_2), 53.5 (CH), 57.4 (CH), 68.3 (CH), 71.8 (C), 122.9, 123.8, 127.5, 129.6, 129.9, 133.3, 138.7, 149.8, 162.5 (Ar-C), 178.6 (C=O), 178.6 (C=O), 181.0 (C=O) ppm; MS (EI): m/z 348 (M-CHO_2, 14%), 228 (100), 227 (36), 171 (24), 145 (36), 119 (56), 92 (43), 91 (25), 77 (22), 44 (14). HRMS (DIP): m/z [M–CHO_2] calculated for $C_{21}H_{22}N_3O_2$: 348.1692; found: 348.1712.

Methyl 1-isobutyl-4,6-dioxo-5-phenyl-3-(thiophen-2-yl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4d): After 19 hours and work up the product was isolated as a red pale solid (301 mg, 73 % yield); column chromatography (*n*-hexane:EtOAc; 6:4); mp: 139 – 143 ºC. IR (ATR) υ_{max}: 1710, 1501, 1384, 1236, 1208, 1177, 1164, 822, 701, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, *J*= 6.4 Hz, 3H), 1.01 (d, *J*= 6.4 Hz, 3H), 1.61-1.75 (m, 2H), 2.03-2.24 (m, 1H), 3.37 (d, *J* = 7.6 Hz, 1H), 3.59 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.85 (s, OCH_3), 5.00 (d, *J* = 9.1 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.6 Hz, 1 Ar-H), 7.11-7.43 (m, 7H, Ar-H) ppm; ^{13}C NMR (101 MHz $CDCl_3$): δ 22.1 (CH_3), 24.3 (CH_3), 24.4 (CH), 43.0 (CH_2), 50.1 (CH), 52.4 (CH_3), 55.5 (CH), 57.9 (CH), 70.0 (C), 125.1, 125.4, 126.2, 127.1, 128.5, 129.0, 131.6, 141.1 (Ar-C), 172.3 (C=O), 173.3 (C=O), 174.6 (C=O) ppm; MS (EI): m/z 369 (M-C_3H_7, 2%), 357 (5), 356 (22), 355 (34), 354 (23), 353 (100), 296 (11), 239 (45), 206 (10), 197 (9), 196 (80), 179 (26), 162 (11), 149 (12) 136 (17), 109 (15). HRMS (DIP): m/z [M^+] calculated for $C_{22}H_{24}N_2O_4S$: 412.1457; found: 412.1469.

Methyl 6a-isobutyl-4,6-dioxo-5-phenyl-2-(thiophen-2-yl)octahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5d): After 36 hours and work up the product was isolated as a sticky yellow oil (175 mg, 44 % yield); column chromatography (silica gel deactivate with 5% Et_3N) (*n*-hexane:EtOAc; 6:4); IR (ATR) υ_{max}: 3340, 2956, 2926, 1708, 1378, 1198, 1139, 843, 689, 597 cm^{-1}; ^1H NMR (300 MHz, MeOD): δ 0.95 (d, *J*= 6.4 Hz, 3H), 1.04 (d, *J*= 6.4 Hz, 3H), 1.71-2.00 (m, 2H), 2.03-2.16 (m, 1H), 3.66 (dd, *J* = 4.7, 2.2 Hz, 1H), 3.89 (d, *J* = 2.3 Hz, 1H), 5.05 (m, 1H), 6.76-6.69 (m, 2H, Ar-H), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1Ar-H), 6.98 (d, *J* = 3.5 Hz, 1Ar-H),

7.25-7.43 (m, 4H, Ar-H) ppm; ^{13}C NMR (75 MHz MeOD): δ 23.9 (CH_3), 24.7 (CH_3), 26.5 (CH), 44.7 (CH_2), 52.5 (CH), 53.5 (CH), 63.7 (CH), 71.9 (C), 121.0, 125.0, 126.2, 127.8, 128.2, 129.8, 133.3, 150.5 (Ar-C), 178.6 (2x C=O), 181.0 (C=O) ppm; MS (EI): m/z 310 (M-$C_4H_8O_2$), 278 (11), 277 (11), 251 (14), 209 (15), 207 (15), 206 (100), 183 (23), 169 (80), 150 (19), 149 (17). HRMS (DIP): m/z [M$^+$] calculated for $C_{22}H_{24}N_2O_4S$: 412.1457; found: 412.1452.

Methyl 1-benzyl-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4e): After 18 hours and work up the product was isolated as a white solid (356 mg, 81 % yield); column chromatography (*n*-hexane:EtOAc; 8:2); mp: 231-234 ºC. IR (ATR) υ_{max}: 1750, 1716, 1493, 1380, 1209, 1178, 1101, 853, 724, 703, 661 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (br s,1H, NH), 3.11 (d, *J* = 13.5 Hz, 1H), 3.49 (d, *J* = 13.3 Hz, 1H), 3.61 (d, *J* = 7.6 Hz, 1H), 3.70 (dd, *J* = 9.4, 7.6 Hz, 1H), 3.86 (s, 3H, OCH_3), 4.96 (d, *J* = 9.4 Hz, 1H), 6.94-7.05 (m, 2H, Ar-H), 7.11-7.18 (m, 2H, Ar-H), 7.25-7.41 (m, 9H, Ar-H), 7.48-7.57 (m, 2H, Ar-H) ppm;^{13}C NMR (101 MHz, $CDCl_3$): δ 40.4 (CH_2), 49.15 (CH), 52.4 (CH_3), 54.3 (CH), 61.3 (CH), 71.3 (C), 126.1, 127.4, 127.6, 128.5, 128.6, 128.6, 128.9, 129.0, 129.5, 131.4, 134.8, 137.2 (Ar-C), 171.5 (C=O), 173.8 (C=O), 174.9 (C=O) ppm; MS (EI): m/z 381 (M-$C_2H_3O_2$, 3%), 350 (22), 349 (100), 202 (14), 170 (13), 143 (11), 91 (15). HRMS (DIP): m/z [M$^+$] calculated for $C_{27}H_{24}N_2O_4$, 440.1736; found: 440.1755.

Methyl 6a-benzyl-4,6-dioxo-2,5-diphenyloctahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5e): After 37 hours and work up the product was isolated as a sticky yellow oil (194 mg, 44 % yield); column chromatography (silica gel deactivate with 5% Et_3N) (*n*-hexane:EtOAc; 8:2); IR (ATR) υ_{max}: 2918, 2849, 1711, 1455, 1377, 1259, 1173, 1028, 732, 700, 691, 587 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.16 (d, *J* = 12.8 Hz, 1H), 3.63 (d, *J* = 12.8 Hz, 1H), 3.67 (dd, *J* = 4.0, 2.9 Hz, 1H), 3.77 (d, *J* = 2.9 Hz, 1H), 3.83 (s, 3H, OCH_3), 4.88 (d, *J* = 4.0 Hz, 1H), 6.37-6.60 (m, 2H, Ar-H), 7.27-7.36 (m, 11H, Ar-H), 7.39-7.45 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 40.7 (CH_2), 50.3 (CH), 53.0 (CH_3), 54.2 (CH), 66.4 (CH), 71.6 (C), 126.4, 126.5, 127.8, 128.2, 128.8, 129.0, 129.1, 130.5, 131.6, 134.9 (Ar-C), 173.1 (C=O), 175.3 (C=O), 178.0 (C=O) ppm; MS (EI): m/z 349 (M-C_7H_7, 14%), 317 (39), 289 (35), 234 (21), 178 (12), 177 (100), 170 (19), 143 (12), 115 (16), 91 (43). HRMS (DIP): m/z [M$^+$] calculated for $C_{27}H_{24}N_2O_4$, 440.1736; found: 440.1697.

Methyl 1-benzyl-4,6-dioxo-5-phenyl-3-(pyridin-2-yl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4f): After 18 hours and work up the product was isolated as a white solid (388 mg, 87 % yield); column chromatography (*n*-hexane:EtOAc; 6:4); mp: 197-200 ºC. IR (ATR) υ_{max}: 1710, 1495, 1395, 1212, 1137, 1104, 1090, 859, 767, 729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 3.11 (d, *J* = 13.7 Hz, 1H), 3.42 (d, *J* = 13.7 Hz, 1H), 3.63-.77 (m, 2H), 3.85 (s, 3H, OCH_3), 4.83 (d, *J* = 8.9 Hz, 1H), 7.04-7.16 (m, 2H, Ar-H), 7.20-7.47 (m, 10H, Ar-H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H, Ar-H), 8.53 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, Ar-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 42.0 (CH_2), 51.4 (CH), 52.7 (CH_3), 57.1 (CH), 64.8 (CH), 73.5 (C), 123.6, 123.7, 126.5, 127.3, 128.5, 128.7, 129.1, 130.2, 131.8, 135.8, 136.9, 149.3, 156.0 (Ar-C), 171.1 (C=O), 174.3 (C=O), 174.9 (C=O) ppm; MS (EI): m/z 382 (M-$C_2H_3O_2$, 4%), 351 (21), 350 (100), 193 (4). 177 (17), 171 (23), 145 (23), 143 (4), 117 (6), 116 (5), 91 (13). HRMS (DIP): m/z [M$^+$] calculated for $C_{26}H_{23}N_3O_4$, 441.1689; found 441.1669.

Methyl 6a-benzyl-4,6-dioxo-5-phenyl-2-(pyridin-2-yl)octahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5f): After 36 hours and work up the product was isolated as a Sticky yellow oil (238 mg, 54 % yield); column chromatography (silica gel deactivate with 5% Et_3N) (*n*-hexane:EtOAc; 6:4); IR (ATR) υ_{max}: 2923, 2853, 1709, 1592, 1378, 1178, 1051, 744, 702, 590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 3.18 (d, *J* = 12.8 Hz, 1H), 3.60 (d, *J* = 12.9 Hz, 1H), 3.87 (s, 3H, OCH_3), 3.89 (d, *J* = 2.0 Hz, 1H), 4.11-4.15 (m, 1H), 5.04 (d, *J* = 2.7 Hz, 1H), 6.48-6.70 (m, 2H, Ar-H), 6.90-7.53 (m, 9H, Ar-H), 7.54 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.66-7.77 (m, 1H, Ar-H), 8.49 (ddd, *J* = 4.9 Hz, 1H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 41.8 (CH_2), 49.9 (CH), 52.5 (CH), 53.19 (CH_3), 67.1 (CH), 72.3 (C), 121.6, 123.1, 126.1, 127.7, 128.6, 128.9, 130.4, 131.5, 135.0, 138.0, 148.7, 159.2 (Ar-C), 173.1 (C=O), 175.2 (C=O), 178.3 (C=O) ppm;MS (EI): m/z 382 (M$^+$-$C_2H_3O_2$, 51%), 350 (100), 235 (14), 177 (19), 171 (22), 145 (24), 119 (28), 117 (19), 93 (21), 92(22), 91 (52), 78 (14), 44 (23). HRMS (DIP): m/z [M$^+$] calculated for $C_{26}H_{23}N_3O_4$, 441.1689; found 441.1698.

Methyl (1S,3R)-1-((1H-indol-3-yl)methyl)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo [3,4-c]pyrrole-1-carboxylate (4gb): After 26 h and work up the product (317 mg, 76 % yield) was crystallised as colourless prisms: mp 232-234 ºC (dec.); IR ν_{max}: 3358, 2981, 2884, 1776, 1732, 1685, 1440, 1387, 1285, 1200, 1103, 1078, 963, 843, 727, 701, 654 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 10.98 (bs, 1H, NH), 7.55 (d, 1H, *J* = 7.88 Hz, Ar-H), 7.36-6.96 (m, 9H, Ar-H), 5.00 (dd, 1H, *J* = 9.40 Hz, 5.16 Hz, 5-H), 3.74 (dd, 1H, *J* = 9.20 Hz, 7.64 Hz, 4-H), 3.69 (s, 3H, O*CH*$_3$), 3.62 (d, 1H, *J* = 7.40 Hz, 3-H), 3.44 (d, 1H, *J* = 14.56 Hz, 6-H), 3.34 (d, 1H, *J* = 14.50 Hz, 6-H'), 2.66 (s, 3H, N*CH*$_3$), 2.36 (d, 1H, *J* = 5.02 Hz, NH) ppm; ^{13}C NMR (100 MHz, DMSO): δ 176.1 (C=O), 174.9 (C=O), 171.7 (C=O), 139.1, 135.9, 127.9 (2 x C), 127.5, 127.4, 127.3 (2 x C), 124.3, 120.9, 118.5, 118.1, 111.4, 107.9, 70.2, 59.7, 53.78, 51.5, 49.0, 30.2, 24.2 ppm; MS (ESI, M+H$^+$): m/z 418.3 (M+H$^+$, 100) ; HRMS (DIP): m/z [M$^+$] calculated for $C_{24}H_{23}N_3O_4$, 417.1694; found: 417.1689.

Methyl (1S,3R)-1-((1H-indol-3-yl)methyl)-4,6-dioxo-5-phenyl-3-(pyridin-2-yl) octahydropyrrolo [3,4-c] pyrrole-1-carboxylate (4gc): After 26 h and work up the product (384 mg, 80 % yield) was isolated as colourless prisms: mp 231-233 ºC (dec.); IR ν_{max}: 3381, 3350, 3061, 2959, 2878, 1779, 1707, 1614, 1591, 1489, 1435, 1384, 1323, 1204, 1178, 1101, 739, 686 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 10.86 (bs, 1H, NH), 8.59-8.57 (m, 1H, Ar-H), 7.85-6.97 (m, 13H, Ar-H), 5.16 (dd, 1H, *J* = 11.22 Hz, 9.26 Hz, 5-H), 3.97 (dd, 1H, *J* = 9.16 Hz, 7.64 Hz, 4-H), 3.89 (d, 1H, *J* = 7.60 Hz, 3-H), 3.79 (d, 1H, *J* = 11.24 Hz, NH), 3.68 (s, 3H, O*CH*$_3$), 3.47 (d, 1H, *J* = 14.68 Hz, 6-H), 3.30 (d, 1H, *J* = 14.60 Hz, 6-H') ppm; ^{13}C NMR (100 MHz, DMSO): δ 175.2 (C=O), 174.4 (C=O), 171.7 (C=O), 156.4, 148.8, 136.8, 135.6, 132.2, 128.8 (2 x C), 128.2, 128.1, 126.7 (2 x C), 124.3, 123.9, 123.3, 120.6, 118.6, 118.2, 111.2, 109.2, 70.0, 63.4, 57.4, 51.8, 51.4, 31.1 ppm; MS (ESI, M+H$^+$): m/z 481.2 (M+H$^+$, 100); HRMS (DIP): m/z [M$^+$] calculated for $C_{28}H_{24}N_4O_4$, 480.1798; found: 480.1702

Methyl(1S,3R)-1-((1H-indol-3-yl)methyl)-5-methyl-4,6-dioxo-3-(pyridin-2-yl) octahydropyrrolo [3,4-c]pyrrole-1-carboxylate (4gd): After 26 h and work up the product (313 mg, 75 % yield) was isolated and crystallised as colourless prisms: mp 229-231 ºC (dec.); IR ν_{max}: 3359, 3300, 2981, 1774, 1735, 1682, 1595, 1443, 1289, 1224, 1095, 995, 727 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 10.82 (bs, 1H, NH), 8.49-8.44 (m, 1H, Ar-H), 7.785-

6.92 (m, 8H, Ar-H), 5.02 (dd, 1H, *J* = 11.04 Hz, 9.32 Hz, 5-H), 3.97 (dd, 1H, *J* = 9.14 Hz, 7.54 Hz, 4-H), 3.67 (s, 3H, OC*H*$_3$), 3.65 (d, 1H, *J* = 7.48 Hz, 3-H), 3.55 (d, 1H, *J* = 11.12 Hz, NH), 3.39 (d, 1H, *J* = 14.92 Hz, 6-H), 3.21 (d, 1H, *J* = 14.84 Hz, 6-H'), 2.61 (s, 3H, NC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 176.0 (C=O), 175.2 (C=O), 171.7 (C=O), 156.4, 148.7, 136.6, 135.5, 128.0, 124.2, 123.7, 123.0, 120.6, 188.5, 118.2, 111.1, 109.1, 72.6, 62.9, 57.0, 51.8, 51.3, 30.9, 24.3 ppm; MS (ESI, M+H$^+$): m/z 419.2 (M+H$^+$, 100); HRMS (DIP): m/z [M$^+$] calculated for $C_{23}H_{22}N_4O_4$, 418.1641; found: 418.1642.

Methyl(1S,3R)-1-((1H-indol-3-yl)methyl)-3-(3-chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo [3,4-c] pyrrole-1-carboxylate (4ge): After 26 h and work up the product (349 mg, 68 % yield) was isolated and crystallised as colourless prisms: mp 273-275 ºC (dec.); IR ν_{max}: 3335, 2981, 1779, 1708, 1598, 1573, 1433, 1385, 1202, 1181, 1100, 954, 748, 689 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 11.02 (bs, 1H, NH), 7.58-6.98 (m, 9H, Ar-H), 5.14 (dd, 1H, *J* = 9.46 Hz, 4.50 Hz, 5-H), 3.91 (dd, 1H, *J* = 9.48 Hz, 7.64 Hz, 4-H), 383 (dd, 1H, *J* = 7.56 Hz, 1.60 Hz, 3-H), 3.66 (s, 3H, OC*H*$_3$), 3.50 (d, 1H, *J* = 14.56 Hz, 6-H), 3.35 (d, 1H, *J* = 14.52 Hz, 6-H'), 2.69 (d, 1H, *J* = 4.36 Hz, NH) ppm; ^{13}C NMR (100 MHz, DMSO): δ 175.3 (C=O), 174.0 (C=O), 171.6 (C=O), 142.0, 135.9, 132.7, 132.0, 129.8, 128.8 (2 x C), 128.2, 127.5 (2 x C), 127.1, 126.5 (2 x C), 126.4, 124.6, 121.0, 118.5, 118.0, 111.4, 107.6, 70.3, 59.0, 53.7, 51.5, 48.7, 30.3 ppm; MS (ESI, M+H$^+$): m/z 512.2 (M+H$^+$, 100), 514.2 (M+H$^+$, 35); HRMS (DIP): m/z [M$^+$] calculated for $C_{29}H_{24}ClN_3O_4$, 513.1455; found: 513.1442

Methyl(1S,3R)-1-((1H-indol-3-yl)methyl)-3-(3-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4gf): After 26 h and work up the product (307 mg, 68 % yield) was isolated and crystallised as colourless prisms: mp 251-253 ºC (dec.); IR ν_{max}: 3339, 3324, 3062, 2949, 2926, 1782, 1704, 1672, 1426, 1290, 1203, 1099, 1081,755, 748 cm^{-1}; ^{1}H NMR (400 MHz, δ 10.99 (bs, 1H, NH), 7.54-6.96 (m, 9H, Ar-H), 5.01 (dd, 1H, *J* = 9.38 Hz, 4.66 Hz, 5-H), 3.75 (dd, 1H, *J* = 9.30 Hz, 7.54 Hz, 4-H), 3.68 (s, 3H, OC*H*$_3$), 3. 62 (dd, 1H, *J* = 7.40 Hz, 1.32 Hz, 3-H), 3.45 (d, 1H, *J* = 14.60 Hz, 6-H), 3.29 (d, 1H, *J* = 14.56 Hz, 6-H') 2.66 (s, 3H, NC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 176.0 (C=O), 174.9 (C=O), 171.5 (C=O), 142.0, 135.9, 132.5, 129.7, 127.4, 127.3, 127.9, 126.0, 124.5, 121.0, 118.5, 118.0, 111.4, 107.7, 70.1, 58.8, 53.4, 51.5, 48.7, 30.2, 24.2 ppm; MS (ESI, M+H$^+$): m/z 452.2 (M+H$^+$, 100), 454.2 (M+H$^+$, 35); HRMS (DIP): m/z [M$^+$] calculated for $C_{24}H_{22}ClN_3O_4$, 451.1299; found: 451.1293.

(1S,3R)-methyl1-((1H-indol-3-yl)methyl)-3-(4-chlorophenyl)-5-ethyl-4,6-dioxo-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4gg): After 26 h and work up the product (340 mg, 73 % yield) was isolated and crystallised as colourless prisms: mp 237-239 ºC (dec.); IR ν_{max}: 3339, 2981, 2944, 2840, 1774 (C=O), 1739 (C=O), 1683 (C=O), 744cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 11.00 (brs, 1H, N*H*), 7.54 (d, 1H, *J*= 7.88 Hz, Ar*H*), 7.35-7.33 (m, 5H, Ar*H*), 7.17-6.96 (m, 3H, Ar*H*), 5.02 (dd, 1H, *J*= 4.68 Hz, *J*= 9.4 Hz, 5*H*), 3.72 (d, 1H, *J*= 7.6 Hz, C*H*HCH$_3$), 3.68(s, 3H, OC*H*$_3$),3.60 (d, 1H, *J*= 7.48 Hz, C*H*HCH$_3$), 3.43 (d, 1H, *J*= 14.6 Hz, 6*H*), 3.30 (d, 1H, *J*= 14.56 Hz, 6'*H*), 3.25-3.13 (m, 2H, 3*H* and N*H*), 3.44 (s, 1H, N*H*), 2.42 (d, 1H, *J*= 3.56 Hz, 4*H*), 0.91(t, 3H, *J*= 7.16 Hz, CH$_2$C*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 175.7 (C=O), 174.6 (C=O), 171.5 (C=O), 138.1, 135.9, 131.8, 129.2 (2 x C), 127.7 (2 x C), 127.5, 124.4, 120.9, 118.5, 118.0, 111.4, 107.8, 70.2, 58.8, 53.4, 51.5, 48.5, 32.9, 30.2, 12.7 ppm; MS (ESI, M+H$^+$): m/z 466.3 (M$^+$, 100, Cl: 35) /468.3 (M$^+$, 33.3, Cl: 37)-(3/1) and 467.3 (M+1, 100, Cl: 35) /469.3(M+1, 33.3, Cl: 37) -(3/1); HRMS (DIP): m/z [M$^+$] calculated for $C_{25}H_{24}ClN_3O_4$, 465.1451; found: 465.1455.

Methyl (2S, 3S, 6aR)-6a-((1H-indol-3-yl)methyl)-5-methyl-4,6-dioxo-2-phenyl octahydro pyrrolo[3,4-b]pyrrole-3-carboxylate (5gb): After 36 h and work up the product (400 mg, 96 % yield) was isolated and crystallised as colourless prisms: mp 151-153 ºC; IR ν_{max}: 3355, 3059, 2981, 2889, 1710, 1595, 1495, 1436, 1383, 1195, 1011, 744 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ11.00 (bs, 1H, NH), 7.70 (d, 1H, *J* = 7.76 Hz, Ar-H), 7.40-7.02 (m, 9H, Ar-H), 4.66 (dd, 1H, *J* = 5.90 Hz, 5.90 Hz, 2-H), 4.06 (d, 1H, *J* = 5.36 Hz, NH), 3.54 (s, 3H, OC*H*$_3$), 3.50 (d, 1H, *J* = 4.96 Hz, 4-H), 3.42 (d, 1H, *J* = 14.20 Hz, 6-H), 3.22 (d, 1H, *J* = 14.24 Hz, 6-H'), 3.12 (dd, 1H, *J* = 6.18 Hz, 5.14 Hz, 3-H), 2.59 (s, 3H, NC*H*$_3$) ppm; **^{13}C** NMR (100 MHz, DMSO): δ 178.9 (C=O), 176.1 (C=O), 171.5 (C=O), 143.9, 135.9, 132.9, 130.0, 127.4, 127.3, 126.2, 125.2, 124.7, 121.0, 118.6, 118.2, 111.5, 107.6, 70.9, 65.3, 54.1, 52.1, 51.1, 28.8, 24.4 ppm; MS (ESI, M+H$^+$): m/z 417.4 (M+H$^+$, 100); HRMS (DIP): m/z [M$^+$] calculated for $C_{24}H_{23}N_3O_4$, 417.1694; found: 417.1688.

Methyl(2S,3S,6aR)-6a-((1H-indol-3-yl)methyl)-4,6-dioxo-5-phenyl-2-(pyridin-2-yl)octahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5gc): After 36 h and work up the product (441 mg, 92 % yield) was isolated and crystallised as colourless prisms: mp 219-221 ºC (dec.); IR ν_{max}: 3352, 3058, 2981, 1712, 1595, 1541, 1436, 1383, 1099, 744 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 10.91 (bs, 1H, NH), 8.72 (brd, 1H, *J* = 4.16 Hz, Ar-H), 7.80-6.94 (m, 13H, Ar-H), 4.45 (dd, 1H, *J* = 8.24 Hz, 8.20 Hz, 2-H), 3.67-3.60 (m, 2H, 3-H, 6-H), 3.43 (s, 3H, OC*H*$_3$), 3.39-3.30 (m, 2H, 4-H, 6-H') ppm; ^{13}C NMR (100 MHz, DMSO): δ 178.8 (C=O), 175.1 (C=O), 172.7 (C=O), 160.2, 148.6, 136.9, 136.0, 131.6, 128.6 (2 x C), 128.2, 127.4, 126.1 (2 x C), 124.7, 122.5, 121.3, 121.1, 118.7, 118.3, 111.6, 107.5, 72.5, 66.9, 52.3, 51.7, 51.1, 20.2 ppm; MS (ESI, M+H$^+$): m/z 481.2 (M+H$^+$, 100); HRMS (DIP): m/z [M$^+$] calculated for $C_{28}H_{24}N_4O_4$, 480.1798; found: 480.1704.

Methyl(2S,3S,6aR)-6a-((1H-indol-3-yl)methyl)-5-methyl-4,6-dioxo-2-(pyridin-2-yl)octahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5gd): After 36 h and work up the product (355 mg, 85 % yield) was isolated and crystallised as colourless prisms: mp 198-200 ºC (dec.); IR ν_{max}: 3355, 2981, 2972, 2889, 1975, 1774, 1698, 1520, 1432, 1380, 1251, 1150, 1073, 955, 775, 741 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 10.97 (bs, 1H, NH), 8.40-8.38 (m, 1H, Ar-H), 7.75-7.67 (m, 2H, Ar-H), 7.47-6.99 (m, 6H, Ar-H), 4.78 (dd, 1H, *J* = 4.74 Hz, 3.34 Hz, 2-H), 4.07 (d, 1H, *J* = 5.36 Hz, NH), 3.79 (dd, 1H, *J* = 3.01 Hz, 2.76 Hz, 3-H), 3.57 (s, 3H, OC*H*$_3$), 3.47 (d, 1H, *J* = 2.64 Hz, 4-H), 3.39 (d, 1H, *J* = 14.08 Hz, 6-H), 3.15 (d, 1H, *J* = 14.08 Hz, 6-H'), 2.33 (s, 3H, NC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 179.5 (C=O), 176.1 (C=O), 172.5 (C=O), 159.9, 148.5, 136.6, 135.8, 127.4, 124.6, 122.3, 121.0, 120.9, 118.6, 118.1, 111.5, 107.6, 72.1, 66.7, 52.2, 51.7, 50.8, 29.5, 24.1 ppm; MS (ESI, M+H$^+$): m/z 419.2 (M+H$^+$, 100). HRMS (DIP): m/z [M$^+$] calculated for $C_{23}H_{22}N_4O_4$, 418.1641; found: 418.1649.

Methyl(2S,3S,6aR)-6a-((1H-indol-3-yl)methyl)-2-(3-chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5ge): After 36 h and work up the product (503 mg, 98 % yield) was isolated and crystallised as colourless prisms: mp 169-171 ºC; IR ν_{max}: 3315, 3060, 2983,

2950, 1782, 1739, 1703, 1595, 1436, 1392, 1253, 1240, 1164, 981, 747 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.08 (bs, 1H, NH), 7.75 (d, 1H, *J* = 7.80 Hz, Ar-H), 7.53-6.64 (m, 13H, Ar-H), 4.78 (dd, 1H, *J* = 5.42 Hz, 5.42 Hz, 2-H), 4.24 (d, 1H, *J* = 5.48 Hz, NH), 3.72 (d, 1H, *J* = 4.44 Hz, 4-H), 3.58 (s, 3H, OC*H*$_3$), 3.55 (d, 1H, *J* = 14.12 Hz, 6-H), 3.43 (dd, 1H, *J* = 5.42 Hz, 4.48 Hz, 3-H), 3.30 (d, 1H, *J* = 14.18 Hz, 6-H') ppm; ^{13}C NMR (100 MHz, DMSO): δ 179.1 (C=O), 176.3 (C=O), 173.1 (C=O), 145.3, 137.5, 134.8, 133.3, 131.0, 129.4 (2 x C), 129.1, 128.7, 128.4, 127.5 (2 x C), 127.4, 126.0, 125.8, 122.5, 120.0, 119.6, 112.4, 109.3, 72.7, 66.6, 55.9, 52.8, 52.5, 30.5. MS (ESI, M-H$^+$): m/z 512.2 (M+H$^+$, 100), 514.2 (M+H$^+$, 35). HRMS (DIP): m/z [M$^+$] calculated for $C_{29}H_{24}ClN_3O_4$, 513.1455; found: 513.1450.

Methyl(2S,3S,6aR)-6a-((1H-indol-3-yl)methyl)-2-(3-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-b]pyrrole-3-carboxylate (5gf): After 26 h and work up the product (429 mg, 95 % yield) was isolated and crystallised as colourless prisms: mp 152-154 ºC ; IR ν_{max}: 3344, 3270, 3060, 2982, 2949, 1780, 1737, 1705, 1378, 1288, 1173, 747, 681 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.00 (bs, 1H, NH), 7.70 (d, 1H, *J* = 7.76 Hz, Ar-H), 7.40-7.02 (m, 8H, Ar-H), 4.66 (dd, 1H, *J* = 5.68 Hz, 5.68 Hz, 2-H), 4.06 (d, 1H, *J* = 5.28 Hz, NH), 3.54 (s, 3H, OC*H*$_3$), 3.50 (d, 1H, *J* = 4.88 Hz, 4-H), 3.43 (d, 1H, *J* = 14.20 Hz, 6-H), 3.22 (d, 1H, *J* = 14.20 Hz, 6-H')), 3.13 (dd, 1H, *J* = 6.36 Hz, 4.96 Hz, 3-H), 2.59 (s, 3H, NC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 178.8 (C=O), 176.1 (C=O), 171.5 (C=O), 143.9, 135.9, 132.9, 130.0, 127.4, 127.3, 126.2, 125.2, 124.7, 121.0, 118.6, 118.2, 111.5, 107.6, 70.9, 65.3, 54.1, 52.1, 51.1, 28.8, 24.1 ppm; MS (ESI, M+H$^+$): m/z 452.2(M+H$^+$, 100), 454.2(M+H$^+$, 35). HRMS (DIP): m/z [M$^+$] calculated for $C_{24}H_{22}ClN_3O_4$, 451.1299; found: 451.1301.

Methyl (2S,3S,3aS,6aR)-6a-((1H-indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-4,6-dioxo-2,5-diphenyloctahydropyrrolo[3,4-b]pyrrole-3-carboxylate (6ga): After 24 h and work up the product (552 mg, 86 % yield) was isolated and crystallised as pale yellow prisms: mp 150-152 ºC; IR ν_{max}**:** 3202, 3060, 2981, 2889, 1787, 1739, 1702, 1537, 1492, 1389, 1252, 1202, 923, 743, 704 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.60 (bs, 1H, NH), 11.33 (bs, 1H, NH), 8.11 (d, 2H, *J* = 7.40 Hz, Ar-H), 7.72-7.00 (m, 17H, Ar-H), 6.80 (bs, 1H, 2-H), 4.22 (d, 1H, *J* = 1.44 Hz, 4-H), 3.91 (brs, 2H, 6-H ve 6-H'), 3.46 (dd, 1H, *J* = 1.76 Hz, 1.76 Hz 3-H), 2.78 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 179.7 (C=S), 176.4 (C=O), 173.9 (C=O), 168.7 (C=O), 165.1 (C=O), 138.5, 135.4, 133.3, 133.0, 130.8, 129.2, 129.6 (2 x C), 129.0 (2 x C), 128.8 (2 x C), 127.8 (2 x C), 127.8, 127.3, 126.5 (2 x C), 126.2, 125.1 (2 x C), 121.1, 118.8, 118.1, 111.4, 104.5, 74.2, 69.2, 54.2, 51.5, 50.1, 26.7 ppm; MS (ESI, M+H$^+$): m/z 643.2 (M+H$^+$, 100); HRMS (DIP): m/z [M$^+$] calculated for $C_{37}H_{30}N_4O_5S$, 642.1937; found: 642.1930.

Methyl (2S,3S,3aS,6aR)-6a-((1H-indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-5-methyl-4,6-dioxo-2-phenyloctahydropyrrolo[3,4-b]pyrrole-3-carboxylate (6gb): After 24 h and work up the product (516 mg, 89 % yield) was isolated and crystallised as pale yellow prisms: mp 207-209 ºC; IR ν_{max}: 3267, 3187, 3060, 3027, 2885, 1786, 1741, 1686, 1546, 1445, 1225, 955, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.74 (bs, 1H, NH), 11.25 (bs, 1H, NH), 8.12 (d, 2H, *J* = 7.24 Hz, Ar-H), 7.73-7.59 (m, 4H, Ar-H), 7.38-6.98 (m, 9H, Ar-H), 6.64 (brs, 1H, 2-H), 3.97 (d, 1H, *J* = 1.84 Hz, 4-H), 3.76 (brs, 2H, 6-H ve 6-H'), 3.24 (dd, 1H, *J* = 2.16 Hz, 2.16 Hz, 3-H), 2.81 (s, 3H, OC*H*$_3$), 2.75 (s, 3H, NC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 178.8 (C=S), 178.0 (C=O), 174.6 (C=O), 168.7 (C=O), 164.9 (C=O), 138.7, 135.4, 133.3, 133.1, 129.1 (2 x C), 128.6 (2 x C), 127.8 (2 x C), 127.7, 127.2, 126.0, 124.8 (2 x C), 121.1, 118.8, 118.0, 111.4, 104.5 74.2, 69.2, 53.9, 51.5, 50.0, 26.2, 25.3 ppm; MS (ESI, M+H$^+$): m/z 580.6 (M+H$^+$, 100); HRMS (DIP): m/z [M$^+$] calculated for $C_{32}H_{28}N_4O_5S$, 580.1780; found: 580.1776.

Methyl (2S,3S,3aS,6aR)-6a-((1H-indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-4,6-dioxo-5-phenyl-2-(pyridin-2-yl)octahydropyrrolo[3,4-b]pyrrole-3-carboxylate (6gc): After 30 h and work up the product (489 mg, 76 % yield) was isolated and crystallised as pale yellow prisms: mp 170-172 ºC; IR ν_{max}: 3357, 2981, 1782, 1755, 1738, 1698, 1538, 1255, 1238, 743,706 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.92 (bs, 1H, NH), 11.33 (bs, 1H, NH), 8.45-8.43 (m, 1H, Ar-H), 8.01-7.06 (m, 18H, Ar-H), 6.56 (brs, 1H, 2-H), 4.25 (s, 1H, 4-H), 3.90 (d, 1H, *J* = 15.06 Hz, 6-H), 3.84 (d, 1H, *J* = 15.12 Hz, 6-H'), 3.24 (s, 1H, 3-H), 2.73 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 176.6 (C=S), 176.5 (C=O), 173.2 (C=O), 167.5 (C=O), 163.6 (C=O), 156.8, 148.2, 135.7, 134.2, 132.0, 131.9, 130.2, 128.1 (2 x C), 128.1, 128.0 (2 x C), 126.6, 126.4 (2 x C), 125.4 (2 x C), 124.9, 122.8, 121.9, 120.0, 117.6, 117.1, 110.2, 103.4, 73.0, 69.5, 53.4, 50.4, 46.4, 25.8 ppm; MS (ESI, M+H$^+$): m/z 644.2 (M+H$^+$, 100); HRMS (DIP): m/z [M$^+$] calculated for $C_{36}H_{29}N_5O_5S$, 643.1889; found: 643.1883.

Methyl (2S,3S,3aS,6aR)-6a-((1H-indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-5-methyl-4,6-dioxo-2-(pyridin-2-yl)octahydropyrrolo[3,4-b]pyrrole-3-carboxylate (6gd): After 24 h and work up the product (453 mg, 78 % yield) was isolated and crystallised as pale yellow prisms: mp 198-200 ºC; IR ν_{max}: 3170, 3060, 2961, 1785, 1755, 1738, 1685, 1553, 1449, 1357, 1233, 1007, 748,705 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.99 (bs, 1H, NH), 11.25 (bs, 1H, NH), 8.41-8.39 (m, 1H, Ar-H), 8.02-8.00 (m, 2H, Ar-H), 7.76-7.60 (m, 5H, Ar-H), 7.37-7.00 (m, 6H, Ar-H), 6.56 (d, 1H, *J* = 1.24 Hz 2-H), 3.99 (d, 1H, *J* = 1.36 Hz, 4-H), 3.35 (brs, 2H, 6-H ve 6-H'), 3.07 (s, 3H, OC*H*$_3$), 3.07-3.05 (m, 1H, 3-H), 2.65 (s, 3H, NC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 178.9 (C=S), 177.5 (C=O), 175.3 (C=O), 168.7 (C=O), 164.7 (C=O), 157.8, 149.4, 136.7, 135.4, 133.2, 133.1, 129.1 (2 x C), 127.7, 127.6 (2 x C), 125.9, 123.6, 122.9, 121.0, 118.8, 118.0, 111.3, 104.7, 74.1, 70.4, 54.5, 51.5, 47.5, 26.5, 25.5. MS (ESI, M+H$^+$): m/z 581.6 (M+H$^+$, 100); HRMS (DIP): m/z [M$^+$] calculated for $C_{31}H_{27}N_5O_5S$, 581.1733; found: 581.1727.

Methyl (2S,3S,3aS,6aR)-6a-((1H-indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-2-(3-chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-b]pyrrole-3-carboxylate (6ge): After 24 h and work up the product (554 mg, 82 % yield) was isolated and crystallised as pale yellow prisms: mp 157-159 ºC; IR ν_{max}: 3387, 3196, 3051, 2956, 1787, 1704, 1529, 1491, 1348, 1255, 1191, 755, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.51 (bs, 1H, NH), 11.31 (bs, 1H, NH), 8.09 (d, 2H, *J* = 7.24 Hz, Ar-H), 7.71-7.03 (m, 17H, Ar-H), 6.69 (bs, 1H, 2-H), 4.22 (d, 1H, *J* = 1.84 Hz, 4-H), 3.91 (brs, 2H, 6-H ve 6-H'), 3.44 (dd, 1H, *J* = 2.30 Hz, 2.30 Hz 3-H), 2.76 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 180.5 (C=S), 175.5 (C=O), 173.8 (C=O), 168.5 (C=O), 165.4 (C=O), 141.5, 135.5, 133.5, 133.3, 132.9, 130.9, 130.6, 129.2, 129.1 (2 x C), 128.9 (2 x C), 127.9 (2 x C), 127.8, 127.4, 126.4 (2 x C), 126.1, 125.2, 124.0, 121.1, 118.8, 118.1, 111.4, 104.5, 74.7, 69.2, 54.1, 51.6, 49.9, 26.7 ppm; MS (ESI M+H$^+$): m/z 678.2 (M+H$^+$, 100),

679.2 ($M+H^+$, 35); HRMS (DIP): m/z [M^+] calculated for $C_{37}H_{29}ClN_4O_5S$, 676.1547; found: 676.1544.

Methyl(2S,3S,3aS,6aR)-6a-((1H-indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-2-(3-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-b]pyrrole-3-carboxylate (6gf): After 24 h and work up the product (538 mg, 84 %) was isolated and crystallised as pale yellow prisms: mp 192-194 ºC; IR ν_{max}: 3384, 3203, 2982, 2951, 1784, 1745, 1693, 1537, 1365, 1352, 1254, 1237, 1213, 752, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.67 (bs, 1H, NH), 11.24 (bs, 1H, NH), 8.10 (d, 2H, *J* = 7.40 Hz, Ar-H), 7.73-7.56 (m, 4H, Ar-H), 7.37-7.23 (m, 4H, Ar-H), 7.11-6.95 (m, 4H, Ar-H), 6.53 (bs, 1H, 2-H), 3.96 (d, 1H, *J* = 1.88 Hz, 4-H), 3.75 (brs, 2H, 6-H ve 6-H'), 3.26 (dd, 1H, *J* = 2.36 Hz, 2.36 Hz 3-H), 2.84 (s, 3H, OC*H*$_3$), 2.74 (s, 3H, NC*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 179.2 (C=S), 177.5 (C=O), 174.5 (C=O), 168.5 (C=O), 165.0 (C=O), 141.4, 135.4, 133.4, 133.2, 133.1, 130.5, 129.0 (2 x C), 127.8 (2 x C), 127.6, 127.3, 125.9, 125.2, 123.5, 121.1, 118.8, 117.9, 111.4, 104.5, 74.5, 69.0, 53.8, 51.6, 49.7, 26.3, 25.3 ppm; MS (ESI, $M+H^+$): m/z 615.2 ($M+H^+$, 100), 616.1 ($M+H^+$, 35); HRMS (DIP): m/z [M^+] calculated for $C_{32}H_{27}ClN_4O_5S$, 614.1391; found: 614.1386.

General Procedure Compound 7gg

To a stirred solution of bicyclic pyrrolidine **4gg** (0,4 g, 0,85mmol) in MeOH (not anhydrous, 20 mL) was added dropwise a solution of sodium methoxide (0,38 g, 2,04 mmol) in dry MeOH (10 mL) over 10 min and the mixture stirred and heated at reflux temperature for 36 h. The solvent was evaporated under reduced pressure, quenched with saturated aqueous ammonium chloride then extracted thrice with CH_2Cl_2. The combined organic solvents were dried over $MgSO_4$ and filtered. The product **7gg** (0,13g, 95%) crystallised from CH_2Cl_2 as colourless solid. Mp 207-209 °C (dec).

(2R,3R,3aR,6aS)-6a-((1H-indol-3-yl)methyl)-2-(4-chlorophenyl)-5-ethyl-4,6-dioxo octahydropyrrolo[3,4-b]pyrrole-3-carboxylic acid (7gg): The product **7gg** (130 mg, 95 % yield) was isolated and crystallised from CH_2Cl_2 as colourless solid: mp: 207-209 °C (dec); IR ν_{max}: 3429, 3304, 3065, 2979, 2934, 2905, 2831, 1770 (C=O), 1724 (C=O), 1675(C=O), 831 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 12.8 (brs, 1H, O*H*), 10.98 (br s, 1H, N*H*), 7.70 (d, 1H, *J*= 7.88 Hz, Ar*H*), 7.42-7.27 (m, 5H, Ar*H*), 7.11-6.96 (m, 3H, Ar*H*), 4.72 (d, 1H, *J*= 6.52 Hz, 5*H*), 3.49 (d, 1H, *J*= 5 Hz, 3*H*),3.44 (s, 1H, N*H*), 3.4 (d, 1H, *J*= 14 Hz, 6*H*), 3.22 (d, 1H, *J*= 13.92 Hz, 6'*H*), 3.15-3.04 (m, 2H, C*H*$_2$CH$_3$), 2.99 (dd, 1H, *J*= 5.16 Hz, *J*= 6.46 Hz, 4*H*), 0.62 (t, 3H, *J*= 7.16 Hz, CH$_2$C*H*$_3$) ppm; ^{13}C NMR (100 MHz, DMSO): δ 178.7 (C=O), 176.1 (C=O), 173.0 (C=O), 140.6, 135.8, 131.8, 128.3 (2 x C), 128.0 (2 x C), 127.3, 124.4, 121.0, 118.6, 118.3, 111.4, 107.7, 71.0, 65.6, 54.7, 51.1, 32.7, 29.1, 11.8 ppm; MS (ESI, $M+H^+$): m/z 452.2 (M^+, 100, Cl: 35) /454.2 (M^+, 33.3, Cl: 37)-(3/1) and 453.2 (M+1, 100, Cl: 35) /455.2(M+1, 33.3, Cl: 37) -(3/1)**;** HRMS (DIP): m/z [M^+] calculated for $C_{24}H_{22}ClN_3O_4$, 451.1299; found: 451.1289.

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